TRANSMITTAL LETTER TO THE UNITED STATES ATTORNEY'S DOCKET NUMBER 50501

DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371 U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/06293	**5 July 2000**	**20 July 1999**

TITLE OF INVENTION: NOVEL CARBOXYLIC ACID DERIVATIVES WITH 5, 6-SUBSTITUTED PYRIMIDINE RING, THEIR PREPARATION AND USE AS ENDOTHELIN RECEPTOR ANTAGONISTS

APPLICANT(S) FOR DO/EO/US Wilhelm AMBERG, Georg KETTSCHAU

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. /X/ This express request to begin national examination procedures (35 U.S.C.371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. /x / A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).

   a./X/ is transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / has been transmitted by the International Bureau.
   c./ / is not required, as the application was filed in the United States Receiving Office (RO/US0).

6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).

   a./ / are transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / have been transmitted by the International Bureau.
   c./ / have not been made; however, the time limit for making such amendments has NOT expired.
   d./ / have not been made and will not be made.

8. / / A translation of the amendments to the claims under PCT Article 19(35 U.S.C. 371(c)(3)).

9. / / An oath or declaration of the inventor(s)(35 U.S.C. 171(c)(4)).

10./ / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11./ / An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12./ / An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13./ / A FIRST preliminary amendment.
/ / A SECOND or SUBSEQUENT preliminary amendment.

14./ / A substitute specification.

15./ / A change of power of attorney and/or address letter.

16./x / Other items or information.
International Search Report
International Preliminary Examination Report

U.S. Appln. No. (If Known)	INTERNATIONAL APPLN. NO. PCT/EP00/ 06293	ATTORNEY'S DOCKET NO. 50501

17. /X/ The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO.....$890.00	**890.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$710.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$740.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO .....$ 1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied pro -visions of PCT Article 33(2)-(4).....$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than / / 20 / /30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

Claims	Number Filed	Number Extra	Rate	
Total Claims	8	-20	X$18.	
Indep.Claims	1	-3	X$84.	
Multiple dependent claim(s)(if applicable)			+280.	
TOTAL OF ABOVE CALCULATION			= **890.**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				
SUBTOTAL			= 890.	
Processing fee of $130. for furnishing the English translation later than / /20 / /30 months from the earliest claimed priority date (37 CFR 1.492(f)).		+		
TOTAL NATIONAL FEE			= **890 .**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) $40.00 per property		=		
TOTAL FEES ENCLOSED			= **$ 890.00**	
			Amount to be refunded: $	
			Charged $	

a./X/ A check in the amount of $ 890.00 to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No._____in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **11-0345**. A duplicate copy of this sheetis enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
KEIL & WEINKAUF
1101 Connecticut Ave., N.W.
Washington, D. C. 20036

/Herbert B Keil/
SIGNATURE

Herbert B. Keil
NAME
Registration No. 18,967

10/031164
JC13 Rec'd PCT/PTO 17 JAN 2002

Novel carboxylic acid derivatives with5,6-substituted pyrimidine ring, their preparation and use as endothelin receptor antagonists

The present invention relates to novel carboxylic acid derivatives, their preparation and use.

Endothelin is a peptide which is composed of 21 aminoacids and is synthesized and released by vascular endothelium. Endothelin exists in three isoforms, ET-1, ET-2 and ET-3. "Endothelin" or "ET" hereinafter refers to one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a strong effect on vessel tone. It is known that this vasoconstriction is caused by binding endothelin to its receptor (Nature, 332, 411-415, 1988; FEBS Letters, 231, 440-444, 1988 and Biochem. Biophys. Res. Commun., 154, 868-875, 1988).

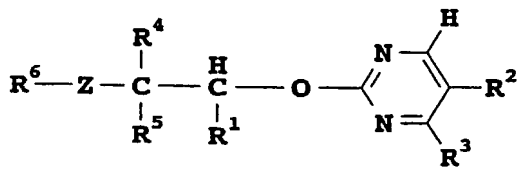
Elevated or abnormal release of endothelin causes persistent vasoconstriction in peripheral, renal and cerebral blood vessels, which may result in disorders. As reported in the literature, endothelin is involved in a number of disorders. These include: hypertension, acute myocardial infarct, pulmonary hypertension, Raynaud's syndrome, cerebral vasospasms, stroke, benign prostate hypertrophy, atherosclerosis, asthma and prostate cancer (J. Vascular Med. Biology 2, 207 (1990), J. Am. Med. Association 264, 2868 (1990), Nature 344, 114 (1990), N. Engl. J. Med. 322, 205 (1989), N. Engl. J. Med. 328, 1732 (1993), Nephron 66, 373 (1994), Stroke 25, 904 (1994), Nature 365, 759 (1993), J. Mol. Cell. Cardiol. 27, A234 (1995); Cancer Research 56, 663 (1996), Nature Medicine 1, 944,(1995)).

At least 2 endothelin receptor subtypes, ET_A and ET_B receptors, are currently described in the literature (Nature 348, 730 (1990), Nature 348, 732 (1990)). Accordingly, substances which inhibit the binding of endothelin to one or both receptors ought to antagonize the physiological effects of endothelin and therefore represent valuable drugs.

The preparation and use of endothelin receptor antagonists has already been described in WO 95/26716, WO 96/11914, WO 97/09294, WO97/12878, WO 97/38980, WO97/38981, WO 97/38982, WO98/09953, WO98/27070, DE 19726146.9, DE 19748238.4, DE 19750529.5, DE 19806438.1, DE 19809144.3 and DE 19836044.4. Further investigation has revealed that related compounds with 5,6-substituted pyrimidine ring has advantageous properties in

relation to receptor affinity and receptor binding profile. The present patent relates to their preparation and use.

The invention relates to carboxylic acid derivatives of the formula I



I

in which R^1 is tetrazolyl or a group

in which R has the following meaning:

a) an OR^7 radical in which R^7 is:

hydrogen, the cation of an alkali metal, the cation of an alkaline earth metal, a physiologically tolerated organic ammonium ion such as tertiary C_1-C_4-alkylammonium or the ammonium ion;

C_3-C_8-cycloalkyl, C_1-C_8-alkyl, CH_2-phenyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, hydroxyl, C_1-C_4-alkoxy, mercapto, C_1-C_4-alkylthio, amino, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl)$_2$;

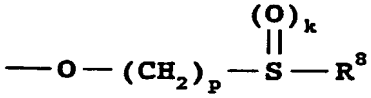
a C_3-C_6-alkenyl or a C_3-C_6-alkynyl group, it being possible for these groups in turn to carry from one to five halogen atoms;

R^7 can also be a phenyl radical which can carry from one to five halogen atoms and/or from one to three of the following radicals: nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, hydroxyl, C_1-C_4-alkoxy, mercapto, C_1-C_4-alkylthio, amino, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl)$_2$;

b) a 5-membered heteroaromatic system, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, which is linked via a nitrogen atom and which may carry from one to two halogen

atoms or from one to two C_1-C_4-alkyl or from one to two C_1-C_4-alkoxy groups;

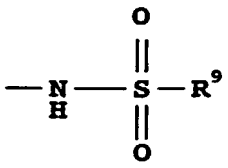
c) a group



in which k has the values 0, 1 and 2, p has the values 1, 2, 3 and 4, and R^8 is

C_1-C_4-alkyl, C_3-C_8-cycloalkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or phenyl which may be substituted by one or more, e.g. from one to three, of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, mercapto, amino, NH(C_1-C_4-alkyl), N(C_1-C_4-alkyl)$_2$;

d) a radical



in which R^9 is:

C_1-C_4-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_8-cycloalkyl, it being possible for these radicals to carry a C_1-C_4-alkoxy, C_1-C_4-alkylthio and/or a phenyl radical as mentioned under c);

phenyl which may be substituted by from one to three of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, mercapto, amino, NH(C_1-C_4-alkyl), N(C_1-C_4-alkyl)$_2$.

The other substituents have the following meanings:

R^2 is hydroxyl, NH_2, NH(C_1-C_4-alkyl), N(C_1-C_4-alkyl)$_2$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio or CR^2 forms together with CR^3 a 5- or 6-membered alkylene or alkenylene ring which may be substituted by one or two C_1-C_4-alkyl groups, in which in each case one or

more methylene groups may be replaced by oxygen, sulfur, -NH or $-N(C_1-C_4\text{-alkyl})$.

R^3 is hydroxyl, NH_2, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, halogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_3-C_6-alkenyloxy, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, $-NH-O-C_1-C_4$-alkyl, C_1-C_4-alkylthio or CR^3 forms, as indicated under R^2, together with CR^2 a 5- or 6-membered ring;

R^4 and R^5 (which may be identical or different) are:

phenyl or naphthyl, each of which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, amino, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$; or

phenyl or naphthyl which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or N-alkyl group;

or C_3-C_7-cycloalkyl;

R^6 is hydrogen,

C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl, it being possible for each of these radicals to be substituted one or more times by: hydroxyl, mercapto, carboxyl, halogen, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkylthio, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl, $(C_1-C_4\text{-alkyl})$NHcarbonyl, $(C_1-C_4\text{-alkyl})_2$Ncarbonyl, C_3-C_8-alkylcarbonylalkyl, amino, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, phenoxy or phenyl, it being possible for said aryl radicals to be substituted one or more times, e.g. from one to three times, by halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, mercapto, carboxy, hydroxyl, amino, R^{10}, C_1-C_4-alkoxycarbonyl, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, methylenedioxy, ethylenedioxy, or phenyl or phenoxy substituted by C_1-C_4-alkylthio;

phenyl or naphthyl, each of which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, NH(C_1-C_4-alkyl), N(C_1-C_4-alkyl)$_2$ or methylenedioxy or ethylenedioxy;

a five- or six-membered heteroaromatic system which contains from one to three nitrogen atoms and/or a sulfur or oxygen atom and which may carry from one to four halogen atoms and/or from one to two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals is turn to carry from one to five halogen atoms and/or from one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

R^{10} is C_1-C_4-alkyl, C_1-C_4-alkylthio or C_1-C_4-alkoxy, each of which carry one of the following radicals: hydroxyl, carboxyl, amino, NH(C_1-C_4-alkyl), N(C_1-C_4-alkyl)$_2$, carboxamide or CON(C_1-C_4-alkyl)$_2$;

Z is sulfur or oxygen.

The following definitions apply herein and hereinafter:

an alkali metal is, for example, lithium, sodium, potassium;

an alkaline earth metal is, for example, calcium, magnesium, barium;

organic ammonium ions are protonated amines such as, for example, ethanolamine, diethanolamine, ethylenediamine, diethylamine or piperazine;

C_3-C_7-cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

C_1-C_4-haloalkyl can be linear or branched such as, for example, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorofluoromethyl, trichloromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl or pentafluoroethyl;

C_1-C_4-haloalkoxy can be linear or branched such as, for example, difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, 1-fluoroethoxy, 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy, 2-fluoroethoxy or pentafluoroethoxy;

C_1-C_4-alkyl can be linear or branched such as, for example, methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl or 2-butyl;

C_2-C_4-alkenyl can be linear or branched such as, for example, ethenyl, 1-propen-3-yl, 1-propen-2-yl, 1-propen-1-yl, 2-methyl-1-propenyl, 1-butenyl or 2-butenyl;

C_2-C_4-alkynyl can be linear or branched such as, for example, ethynyl, 1-propyn-1-yl, 1-propyn-3-yl, 1-butyn-4-yl or 2-butyn-4-yl;

C_1-C_4-alkoxy can be linear or branched such as, for example, methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy or 1,1-dimethylethoxy;

C_3-C_6-alkenyloxy can be linear or branched such as, for example, allyloxy, 2-buten-1-yloxy or 3-buten-2-yloxy;

C_3-C_6-alkynyloxy can be linear or branched such as, for example, 2-propyn-1-yloxy, 2-butyn-1-yloxy or 3-butyn-2-yloxy;

C_1-C_4-alkylthio can be linear or branched such as, for example, methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methylpropylthio or 1,1-dimethylethylthio;

C_1-C_4-alkylcarbonyl can be linear or branched such as, for example, acetyl, ethylcarbonyl or 2-propylcarbonyl;

C_1-C_4-alkoxycarbonyl can be linear or branched such as, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl or n-butoxycarbonyl;

C_3-C_8-alkylcarbonylalkyl can be linear or branched such as, for example, 2-oxoprop-1-yl, 3-oxobut-1-yl or 3-oxobut-2-yl;

C_1-C_8-alkyl can be linear or branched such as, for example, C_1-C_4-alkyl, pentyl, hexyl, heptyl or octyl;

halogen is, for example, fluorine, chlorine, bromine, iodine.

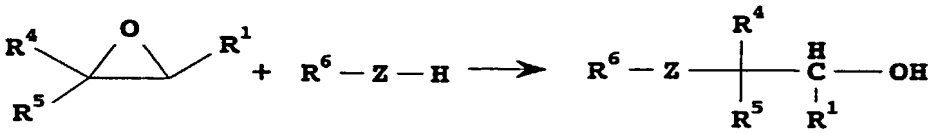
The invention further relates to compounds from which the compounds of the formula I can be released (called prodrugs).

Preferred prodrugs are those in which the release occurs under conditions prevailing in certain compartments of the body, for example in the stomach, intestine, blood stream, liver.

The compounds and the intermediates for their preparation, such as, for example, II and IV, may have one or more asymmetric substituted carbon atoms. Compounds of this type may be in the form of pure enantiomers or pure diastereomers or a mixture thereof. The use of an enantiomerically pure compound as active ingredient is preferred.

The invention further relates to the use of the abovementioned carboxylic acid derivatives for producing drugs, in particular for producing inhibitors of endothelin receptors.

The compounds of the general formula IV in which Z is sulfur or oxygen (IV) can be prepared as described in WO 96/11914.



II III IV

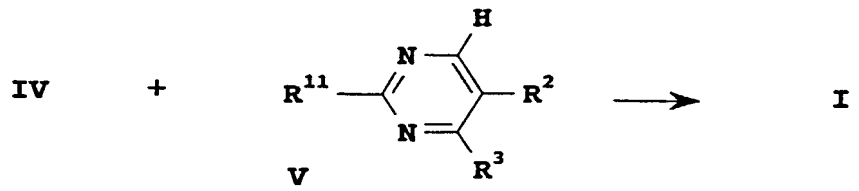
Compounds of the general formula III are either known or can be synthesized, for example, by reducing the corresponding carboxylic acids or their esters, or by other generally known methods.

Compounds of the formula IV can be obtained in enantiomerically pure form by an acid-catalysed transetherification as described in WO 98/09953.

The enantiomerically pure compounds of the formula IV can also be obtained by carrying out a conventional racemate resolution with racemic or diastereomeric compounds of the formula IV, using suitable enantiomerically pure bases. Examples of suitable bases of this type are 4-chlorophenylethylamine and the bases mentioned in WO 96/11914. -

The novel compounds in which the substituents have the meanings stated for general formula I can be prepared, for example, by reacting the carboxylic acid derivatives of the general formula

IV in which the substituents have the stated meaning with compounds of the general formula V.



V is halogen or R^{12}-SO_2-, where R^{12} can be C_1-C_4-alkyl, C_1-C_4-haloalkyl or phenyl. The reaction preferably takes place in an inert solvent or diluent with the addition of a suitable base, i.e. of a base that deprotonates the intermediate IV, at a temperature in the range from room temperature to the boiling point of the solvent.

If R^1 is an ester, then the compounds with R^1 = COOH can be prepared by acidic, basic or catalytic cleavage of the ester group.

Compounds of type I with R^1 = COOH may furthermore be obtained directly when the intermediate IV in which R^1 means COOH is deprotonated with two equivalents of a suitable base and reacted with compounds of the general formula V. Here too, the reaction takes places in an inert solvent and in a temperature range from room temperature to the boiling point of the solvent.

Examples of such solvents or diluents are aliphatic, alicyclic and aromatic hydrocarbons, each of which may optionally be chlorinated, such as, for example, hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride, chloroform, carbon tetrachloride, ethyl chloride and trichloroethylene, ethers such as, for example, diisopropyl ether, dibutyl ether, methyl tert-butyl ether, propylene oxide, dioxane and tetrahydrofuran, nitriles such as, for example, acetonitrile and propionitrile, amides such as, for example, dimethylformamide, dimethylacetamide and N-methylpyrrolidone, sulfoxides and sulfones, such as, for example, dimethyl sulfoxide and sulfolane.

Compounds of the formula V are known, and some of them can be bought, or they can be prepared in a generally known manner. The base which can be used is an alkali metal or alkaline earth metal hydride such as sodium hydride, potassium hydride or calcium hydride, a carbonate such as alkali metal carbonate, e.g. sodium carbonate or potassium carbonate, an alkali metal or

alkaline earth metal hydroxide such as sodium hydroxide or potassium hydroxide, an organometallic compound such as butyllithium or an alkali metal amide such as lithium diisopropylamide.

Compounds of the formula I can also be prepared by starting from the corresponding carboxylic acids, i.e. compounds of the formula I in which R^1 is COOH, and converting these in a conventional way into an activated form such as an acid halide, an anhydride or imidazolide, and then reacting the latter with an appropriate hydroxyl compound HOR^7. This reaction can be carried out in the conventional solvents and often requires addition of a base such as, for example, triethylamine, pyridine, imidazole or diazabicycloundecene. These two steps can also be simplified, for example, by allowing the carboxylic acid to act in the presence of a dehydrating agent such as a carbodiimide on the hydroxyl compound.

It is also possible to prepare compounds of the formula I by starting from the salts of the corresponding carboxylic acids, i.e. from compounds of the formula I in which R^1 is a COOM group where M can be an alkali metal cation or the equivalent of an alkaline earth metal cation. These salts can be reacted with many compounds of the formula R^7-A where A is a conventional nucleofugic leaving group, for example halogen such as chlorine, bromine, iodine or optionally halogen-, alkyl- or haloalkyl-substituted aryl- or alkylsulfonyl such as, for example, toluenesulfonyl and methylsulfonyl or another equivalent leaving group. Compounds of the formula R^7-A with a reactive substituent A are known or can easily be obtained with general expert knowledge. This reaction can be carried out in the conventional solvents and is advantageously undertaken with the addition of a base, in which case those mentioned above are suitable.

In some cases it is necessary to apply generally known protective group techniques for preparing the novel compounds I. If, for example, R^6 = 4-hydroxyphenyl, the hydroxyl group can firstly be protected as benzyl ether, which is then cleaved at a suitable stage in the reaction sequence.

Compounds of the formula I in which R^1 is tetrazolyl can be prepared as described in WO 96/11914.

With a view to the biological effect, preferred carboxylic acid derivatives of the general formula I are those - either as pure enantiomers or pure diastereomers or as mixture thereof - in

which the substituents have the following meanings:

R^2 hydroxyl, $N(C_1-C_4\text{-alkyl})_2$, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio or CR^2 forms together with CR^3 a 5- or 6-membered alkylene or alkenylene ring which may be substituted by one or two C_1-C_4-alkyl groups and in which in each case one or more methylene groups may be replaced by oxygen, sulfur, -NH or $-N(C_1-C_4\text{-alkyl})$;

R^3 hydroxyl, $N(C_1-C_4\text{-alkyl})_2$, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, halogen or CR^3 forms, as indicated for R^2, together with CR^2 a 5- or 6-membered ring;

R^4 and R^5 phenyl or naphthyl, each of which may be substituted by one or more, e.g. from one to three, of the following radicals: halogen, cyano, hydroxyl, mercapto, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl;

phenyl or naphthyl which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or $N(C_1-C_4\text{-alkyl})$ group,

or C_3-C_7-cycloalkyl;

R^6 C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl, it being possible for each of these radicals to be substituted one or more times by: halogen, hydroxyl, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkylthio, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, hydroxycarbonyl, C_1-C_4-alkoxycarbonyl, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, phenoxy or phenyl, it being possible for said aryl radicals to be substituted one or more times, e.g. from one to three times by halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, R^{10}, C_1-C_4-alkoxycarbonyl, methylenedioxy, ethylenedioxy, C_1-C_4-alkylthio, phenyl or phenoxy;

phenyl or naphthyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$;

a five- or six-membered heteroaromatic system which contains from one to three nitrogen atoms and/or one sulfur or oxygen atom and which may carry from one to four halogen atoms and/or from one to two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry from one to five halogen atoms and/or from one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

R^{10} C_1-C_4-alkyl, C_1-C_4-alkoxy, which carry one of the following radicals: hydroxyl, carbamoyl or $CON(C_1$-C_4-alkyl$)_2$;

Z sulfur or oxygen.

Particularly preferred compounds of the formula I are those - either as pure enantiomers or pure diastereomers or as mixture thereof - in which the substituents have the following meanings:

R^2 C_1-C_4-alkyl, C_1-C_4-alkoxy, in particular methyl, ethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy or CR^2 forms together with CR^3 a 5-membered alkylene or alkenylene ring which may be substituted by one or two methyl groups and in which in each case one or more methylene groups may be replaced by oxygen or sulfur;

R^3 C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, in particular methyl, ethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy or CR^3 forms, as indicated for R^2, together with CR^2 a 5-membered ring;

R^4 and R^5 phenyl (identical or different) which may be substituted by one or more, e.g. from one to three, of the following radicals: halogen, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio or

R^4 and R^5 are phenyl groups which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or $N(C_1$-C_4-alkyl) group; or

R^4 and R^5 are cyclohexyl;

R^6 C_1-C_8-alkyl, C_3-C_6-alkenyl or C_3-C_8-cycloalkyl, it being possible for each of these radicals to be substituted one or more times by: halogen, hydroxyl, cyano, C_1-C_4-alkoxy,

C_3-C_6-alkenyloxy, C_1-C_4-alkylthio, phenoxy or phenyl, it being possible for said aryl radicals to be substituted one or more times, e.g. from one to three times, by C_1-C_4-alkyl, C_1-C_4-alkoxy, methylenedioxy, ethylenedioxy, C_1-C_4-alkylthio;

phenyl or naphthyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino or C_1-C_4-dialkylamino;

a five- or six-membered heteroaromatic system which contains one nitrogen atom and/or one sulfur or oxygen atom and which may carry from one to four halogen atoms and/or from one to two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry from one to five halogen atoms and/or from one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy and/or C_1-C_4-alkylthio;

Z sulfur or oxygen.

The compounds of the present invention offer a novel therapeutic potential for the treatment of hypertension, pulmonary hypertension, myocardial infarct, angina pectoris, arrhythmia, acute/chronic renal failure, chronic heart failure, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, atherosclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty and by-pass operations, benign prostate hyperplasia, cirrhosis of the liver, erectile dysfunction, ischemic and intoxication-induced renal failure or hypertension, metastasis and growth of mesenchymal tumors, contrast medium-induced renal failure, pancreatitis, in particular acute pancreatitis, gastrointestinal ulcers.

The invention further relates to combinations of endothelin receptor antagonists of the formula I and inhibitors of the renin-angiotensin system. Inhibitors of the renin-angiotensin system are renin inhibitors, angiotensin II antagonists and angiotensin converting enzyme (ACE) inhibitors. Combinations of endothelin receptor antagonists of the formula I and ACE inhibitors are preferred.

The invention further relates to combinations of endothelin receptor antagonists of the formula I and beta-blockers.

The invention further relates to combinations of endothelin receptor antagonists of the formula I and diuretics.

The invention further relates to combinations of endothelin receptor antagonists of the formula I and substances which block the action of VEGF (vascular endothelial growth factor). Examples of such substances are antibodies directed against VEGF or specific binding proteins or else low molecular weight substances which are able specifically to inhibit the VEGF release or receptor binding.

The aforementioned combinations may be administered simultaneously or sequentially. They can be employed either in a single pharmaceutical formulation or else in separate formulations. The form of administration may also differ, for example the endothelin receptor antagonists may be administered orally and the VEGF inhibitors parenterally.

These combination products are particularly suitable for treating and preventing hypertension and its sequelae, and for treating heart failure.

The good effect of the compounds can be shown in the following tests:

Receptor-binding studies

Cloned human ET_A or ET_B receptor-expressing CHO cells were employed for binding studies.

Membrane preparation

The ET_A or ET_B receptor-expressing CHO cells were grown in DMEM NUT MIX F_{12} medium (Gibco, No. 21331-020) with 10% fetal calf serum (PAA Laboratories GmbH, Linz, No. A15-022), 1 mM glutamine (Gibco No. 25030-024), 100 U/ml penicillin and 100 µg/ml streptomycin (Sigma No. P-0781). After 48 hours, the cells were washed with PBS and incubated with 0.05% trypsin-containing PBS at 37°C for 5 minutes. This was followed by neutralization with medium, and the cells were collected by centrifugation at 300 x g.

For membrane preparation, the cells were adjusted to a concentration of 10^8 cells/ml of buffer (50 mM Tris-HCl buffer, pH 7.4) and then disintegrated with ultrasound (Branson Sonifier 250, 40-70 seconds/constant output 20).

Binding assays

For the ET_A and ET_B receptor-binding assay, the membranes were suspended in incubation buffer (50 mM Tris-HCl, pH 7.4 with 5 mM $MnCl_2$, 40 mg/ml bacitracin and 0.2% BSA) in a concentration of 50 µg of protein per assay mixture and incubated with 25 pM [^{125}I]-ET_1 (ET_A receptor assay) or 25 pM [^{125}I]-ET_3 (ET_B receptor assay) in the presence and absence of test substance at 25°C. The nonspecific binding was determined using 10^{-7} M ET_1. After 30 min, filtration through GF/B glass fiber filters (Whatman, England) in a Skatron cell harvester (Skatron, Lier, Norway) separated free and bound radio ligand, and the filters were washed with ice-cold Tris-HCl buffer, pH 7.4 with 0.2% BSA. The radioactivity collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

Functional vessel test for endothelin receptor antagonists

After pretensioning segments with rabit aorta 2 g and a relaxation time of 1 h in Krebs-Henseleit solution at 37°C and a pH between 7.3 and 7.4, initially a contraction is induced with K^+. After washing out, an endothelin dose-effect plot is constructed up to the maximum.

Potential endothelin antagonists are administered to other specimens of the same vessel 15 min before starting the endothelin dose-effect plot. The effects of the endothelin are calculated as a % of the K^+ contraction. With effective endothelin antagonists there is a rightward shift in the endothelin dose-effect plot.

Testing of ET antagonists *in vivo*:

Male SD rats weighing 250 - 300 g were anesthetized with amobarbital, artificially ventilated, vagotomized and pithed. The carotid artery and jugular vein were catheterized.

In control animals, intravenous administration of 1 µg/kg ET1 results in a marked rise in blood pressure which persists for a lengthy period.

The test animals received i.v. injection (1 ml/kg) of the test compounds 30 min before administration of ET1. To determine the ET-antagonistic properties, the changes in blood pressure in the test animals were compared with those in the control animals.

Oral testing of mixed ET_A and ET_B receptor antagonists:

Male normotensive rats (Sprague Dawley, Janvier) weighing 250-350 g are pretreated with the test substances orally. 80 minutes later, the animals are anesthetized with urethane, and the carotid artery (for measuring the blood pressure) and the jugular vein (administration of big endothelin/endothelin 1) are catheterized.

After a stabilization period, big endothelin (20 µg/kg, admin. vol. 0.5 ml/kg) or ET1 (0.3 µg/kg, admin. vol. 0.5 ml/kg) is given intravenously. Blood pressure and heart rate are recorded continuously for 30 minutes. The marked and long-lasting changes in blood pressure are calculated as the area under the curve (AUC). To determine the antagonistic effect of the test substances, the AUC for the animals treated with substance is compared with the AUC for the control animals.

The novel compounds can be administered orally or parenterally (subcutaneously, intravenously, intramuscularly, intraperitoneally) in a conventional way. Administration can also take place with vapors or sprays through the nasopharyngeal space.

The dosage depends on the age, condition and weight of the patient and on the mode of administration. As a rule, the daily dose of active ingredient is from about 0.5 to 50 mg/kg of body weight on oral administration and from about 0.1 to 10 mg/kg of body weight on parenteral administration.

The novel compounds can be administered in conventional solid or liquid pharmaceutical forms, e.g. as uncoated or (film-)coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active ingredients can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, bulking agents, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellant gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The administration forms obtained in this way normally contain from 0.1 to 90% by

weight of active ingredient.

Synthesis Examples

Example 1

2-Methylsulfanyl-6,7-dihydro-5H-cyclopentapyrimidine

4.9 g (44 mmol) of 2-oxocyclopentanecarbaldehyde, dissolved in 100 ml of water, were added over the course of one hour to a solution of 16.4 g of potassium carbonate (119 mmol) and 42.3 g of S-methylisothiourea sulfate (152 mmol) and, after stirring at room temperature overnight, heated at 65°C for 6 hours. The aqueous solution was extracted with pentane, the organic phase was concentrated, and the residue was chromatographed on silica gel (heptane/ethyl acetate 8:2), resulting in 0.93 g of the target compound as a solid.

Example 2

2-Methylsulfonyl-6,7-dihydro-5H-cyclopentapyrimidine

A solution of 9.9 g (16.1 mmol) of Oxone in 70 ml of water and 4M sodium hydroxide solution were added alternately to a solution of 0.85 g (5.1 mmol) of 2-methylsulfanyl-6,7-dihydro-5H-cyclopentapyrimidine in 20 ml of methanol at 0°C so that a pH of 2-3 was maintained. After the addition was complete, the mixture was stirred at room temperature for 2 hours and then extracted with ethyl acetate, the organic phase was dried over sodium sulfate and evaporated. The solid residue (0.93 g) was employed without further purification.

Example 3

Benzyl 2-(6,7-dihydro-5*H*-cyclopentapyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate

0.6 g (1.6 mmol) of benzyl 2-hydroxy-3-methoxy-3,3-diphenyl-propionate, dissolved in DMF, was added dropwise to a suspension of 0.1 g of NaH (3.3 mmol, 80% in white oil) in 10 ml of DMF at 0°C. After the mixture had been stirred for 30 minutes, 420 mg (2.1 mmol) of 2-methylsulfonyl-6,7-dihydro-5H-cyclopentapyrimidine in 10 ml of DMF were added, and the mixture was stirred at room temperature overnight. It was then poured into ice-water and extracted three

times with diethyl ether. The ether phases were dried with magnesium sulfate and then filtered, and the solvent was stripped off in vacuo. The yellow residue (0.54 g) was chromatographed on silica gel, allowing 243 mg of the required product to be isolated.

MS (API): 503 $(M+Na)^+$

Example 4

2-(6,7-Dihydro-5*H*-cyclopentapyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid (I-136)

A solution of 0.23 g of benzyl 2-(6,7-dihydro-5*H*-cyclopentapyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate in 15 ml of ethyl acetate/methanol 2:1 was hydrogenated with hydrogen under atmospheric pressure, using 60 mg of palladium in active carbon (10%), at room temperature for 24 hours. The mixture was filtered and concentrated, and the residue (177 mg) was stirred into diethyl ether, filtered and then dried. 95 mg of the target product were isolated.

1H-NMR (d_6-DMSO, 200 MHz): 8.3 (s, 1H), 7.2-7.4 (m, 10H); 6.15 (s, 1H); 3.3 (s, 3H); 2.8 (m, 4H), 2.1 (m, 2H).

Example 5

2-Chloro-4-methoxy-5-methylpyrimidine

A solution of 25 g of 2,4-dichloro-5-methylpyrimidine in methanol was cooled to 0°C, 28.5 ml of sodium methoxide solution (30% in methanol) were added, and the mixture was stirred firstly at 0°C for one hour and then at room temperature for 2 hours. The resulting suspension was then freed of solvent, taken up in water and extracted with ether. The organic phases were dried over sodium sulfate, filtered and then concentrated, and the resulting residue was chromatographed on silica gel, resulting in 11.4 g of the target compound.

Example 6

2-(4-Methoxy-5-methylpyrimidin-2-yloxy)-3-isopropoxy-3,3-diphenylpropionic acid (I-5)

0.76 g (2.5 mmol) of 2-hydroxy-3-isopropoxy-3,3-diphenyl-propionic acid, dissolved in DMF, was added dropwise to a suspension of 0.23 g of sodium

hydride (7.6 mmol, 80% in white oil) in 20 ml of DMF at 0°C. After the mixture had been stirred for 30 minutes, 0.6 g (3.8 mmol) of 2-chloro-4-methoxy-5-methylpyrimidine in 10 ml of DMF was added, then the mixture was stirred firstly at room temperature overnight and then at 40°C for 8 hours. It was then poured into ice-water, adjusted to pH 1 with 2N HCl and extracted three times with diethyl ether. The ether phases were extracted with 1N KOH, and the alkaline aqueous phase was again adjusted to pH 1 with 2N HCl and reextracted with ether. The ether phases obtained in this way were dried over magnesium sulfate and filtered, and the solvent was stripped off in vacuo. The yellowish residue (0.8 g) was chromatographed on silica gel, allowing 0.19 g of the required product to be isolated.

1H-NMR ($CDCl_3$, 200 MHz): 8.0 (s, 1H); 7.5-7.6 (m, 2H); 7.2-7.4 (m, 8H); 6.3 (s, 1H); 3.9 (m, 1H); 3.9 (s, 3H); 2.0 (s, 3H); 1.1 (m, 6H).

MS (API): 423 $(M+H)^+$

Example 7

2-Methylsulfanyl-4-methoxy-5-methylpyrimidine

7.2 g (102 mmol) of sodium thiomethanolate were added to a solution of 14.8 g (93 mmol) of 2-chloro-4-methoxy-5-methylpyrimidine in 100 ml of acetonitrile, and the resulting suspension was refluxed for four hours. The solvent was then removed and the residue was taken up in water and extracted with ether. The organic phases were dried over sodium sulfate, filtered and concentrated, and the resulting residue (13.4 g) was reacted without further purification.

Example 8

2-Methylsulfanyl-4-methoxy-5-methylpyrimidine

A solution of 62.4 g (101 mmol) of Oxone in water and 4 M sodium hydroxide solution (about 40 ml) were added to a solution of 13.3 g (78.1 mmol) of 2-methylsulfanyl-4-methoxy-5-methylpyrimidine in 80 ml of methanol at 0°C in such a way that a pH of 2-3 was maintained. After the addition was complete, the mixture was stirred at room temperature for 2 hours and, after removal of methanol, extracted with ethyl acetate, and the organic phase was dried over sodium sulfate and evaporated. The solid residue (14.7 g) was stirred in diethyl ether for two hours, then filtered and dried, resulting

in 13.5 g of pure target product.

Example 9

2-(4-Methoxy-5-methylpyrimidin-2-yloxy)-3-benzyloxy-3,3-diphenyl-propionic acid (I-47)

1.0 g (2.5 mmol) of 2-hydroxy-3-benzyloxy-3,3-diphenylpropionic acid, dissolved in DMF, was added dropwise to a suspension of 0.27 g of sodium hydride (9 mmol, 80% in white oil) in 20 ml of DMF at 0°C. After stirring the mixture for 30 minutes, 0.79 g (3.9 mmol) of 2-methylsulfonyl-4-methoxy-5-methylpyrimidine in 10 ml of DMF were added, and the mixture was then stirred at room temperature overnight. It was poured into ice-water, adjusted to pH 1 with 2N HCl and extracted three times with diethyl ether. The ether phases were extracted with 1N KOH, and the alkaline aqueous phase was again adjusted to pH 1 with 2N HCl and extracted with ether. The resulting ether phases were dried over magnesium sulfate and filtered, and the solvent was stripped off in vacuo. The yellowish residue (1.2 g) was mixed with 10 ml of diethyl ether and stirred at room temperature for 3 hours, and then the precipitated solid was filtered off with suction and dried, resulting in 0.6 g of the target compound.

^{1}H-NMR ($CDCl_3$, 200 MHz): 8.0 (s, 1H), 7.2-7.45 (m, 10H); 6.2 (s, 1H); 4.7 (d, 1H); 4.55 (d, 1H); 3.85 (s, 3H); 2.1 (s, 3H).

MS (API): 471 $(M+H)^+$

Example 10

2-(4-Methoxy-5-methylpyrimidin-2-yloxy)-3-hydroxy-3,3-diphenyl-propionic acid (I-29)

A solution of 440 mg (0.94 mmol) of 2-(4-methoxy-5-methylpyrimidin-2-yloxy)-3-benzyloxy-3,3-diphenyl-propionic acid in 20 ml of ethyl acetate was hydrogenated with hydrogen under atmospheric pressure at room temperature using 80 mg of palladium on active carbon (10%) for 3 days. The mixture was filtered and concentrated, and the residue (430 mg) was chromatographed on silica gel, allowing 39 mg of the desired target product to be isolated.

^{1}H-NMR (d_6-DMSO, 200 MHz): 8.0 (s, 1H); 7.6 (m, 2H); 7.0-7.5 (m, 8H); 5.6 (s, 1H); 3.8 (s, 3H); 1.9 (s, 3H).

Example 11

(*S*)-2-(4-Methoxy-5-methylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid (I-2)

10 g (36.7 mmol) of (*S*)-2-hydroxy-3-methoxy-3,3-diphenyl-propionic acid, dissolved in 40 ml of DMF, were added dropwise to a suspension of 3.3 g of sodium hydride (110 mmol, 80% in white oil) in 40 ml of DMF at 0°C. After stirring the mixture for 60 minutes, 9.6 g (47.7 mmol) of 2-methylsulfonyl-4-methoxy-5-methylpyrimidine in 20 ml of DMF were added, and the mixture was then stirred at room temperature overnight. It was poured into ice-water, adjusted to pH 1 with 2N HCl and extracted three times with diethyl ether. The ether phases were extracted with 1N KOH, and the alkaline aqueous phase was readjusted to pH 1 with 2N HCl and extracted with ether. The resulting ether phases were dried over sodium sulfate and filtered, and the solvent was stripped off in vacuo. The residue (17.1 g) was stirred in diethyl ether overnight, filtered and dried. The solid (12.1 g) obtained in this way was chromatographed on silica gel, allowing 11.4 g of the desired product to be isolated.

1H-NMR ($CDCl_3$, 270 MHz): 8.0 (s, 1H), 7.2-7.45 (m, 10H); 6.1 (s, 1H); 3.85 (s, 3H); 3.3 (s, 3H); 2.0 (s, 3H).

m.p.: 134°C (decomposition)

MS (ESI): 394 $(M+H)^+$

The following compounds were prepared analogously to the abovementioned examples

Example 12

3-Ethoxy-2-(4-methoxy-5-methylpyrimidin-2-yloxy)-3,3-diphenyl-propionic acid (I-4)

1H-NMR ($CDCl_3$, 200 MHz): 8.0 (s, 1H), 7.1-7.5 (m, 10H); 6.2 (s, 1H); 3.9 (s, 3H); 3.5 (m, 2H); 2.0 (s, 3H); 1.1 (t, 3H).

MS (API): 409 $(M+H)^+$

Example 13

3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-(4-methoxy-5-methylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid

1H-NMR ($CDCl_3$, 200 MHz): 8.0 (s, 1H), 7.1-7.4 (m, 10H); 6.6-6.8 (m, 3H); 6.3 (s, 1H); 3.9 (s, 3H); 3.8 (m, 7H); 3.5-3.65 (m, 1H); 2.7-2.9 (m, 2H); 2.0 (s, 3H); 1.1 (t, 3H).

MS (ESI): 555 $(M+H)^+$

Example 14

3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-(9-methyl-9*H*-purin-2-yloxy)-3,3-diphenylpropionic acid (I-150)

1H-NMR ($CDCl_3$, 200 MHz): 8.2 (s, 1H); 7.9 (s, 1H), 7.1-7.4 (m, 10H); 6.6-6.8 (m, 3H); 6.3 (s, 1H); 3.9 (s, 3H); 3.8 (m, 7H); 3.5-3.65 (m, 1H); 2.7-2.9 (m, 2H); 2.0 (s, 3H); 1.1 (t, 3H).

MS (ESI): 555 $(M+H)^+$

Example 15

3,3-Bis(4-fluorophenyl)-3-methoxy-2-(4-methoxy-5-methylpyrimidin-2-yloxy)propionic acid (I-61)

1H-NMR ($CDCl_3$, 400 MHz): 8.0 (s, 1H), 7.4-7.5 (m, 2H); 7.25-7.35 (m, 2H); 6.9-7.0 (m, 4H); 6.05 (s, 1H); 3.9 (s, 3H); 3.3 (s, 3H); 2.05 (s, 3H).

MS (API): 431 $(M+H)^+$

Example 16

3-(3,4-Dimethylbenzyloxy)-2-(4-methoxy-5-methylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid (I-149)

1H-NMR ($CDCl_3$, 200MHz): 8.0 (s, 1H), 7.1-7.5 (m, 10H); 6.2 (s, 1H); 4.6 (d, 1H); 4.4 (d, 1H); 3.85 (s, 3H); 2.2 (s, 6H); 2.0 (s, 3H).

MS (API): 498 $(M+H)^+$

The compounds listed in Table 1 can be prepared analogously.

Example 17

Receptor binding data were measured using the binding assay described above for the compounds listed below.

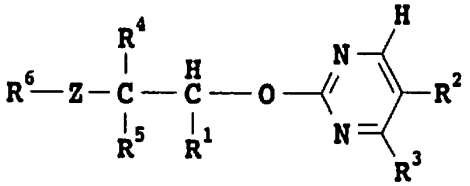
The results are shown in Table 2.

Table 2

Receptor binding data (K_i values)

Compound	ET_A [nM]
I-2	0.6
I-4	1.8
I-5	3
I-29	175
I-47	8.7
I-61	3.1
I-136	22
I-149	5
I-150	2200

Table I



I

No.	R^1	R^4, R^5	R^6	R^2	R^3	Z
I-1	$COOCH_3$	Phenyl	Methyl	Me	OMe	O
I-2	COOH	Phenyl	Methyl	Me	OMe	O
I-3	COOH	Phenyl	CH_3–S–CH_2–CH_2–	Me	OMe	O
I-4	COOH	Phenyl	Ethyl	Me	OMe	O
I-5	COOH	Phenyl	iso–Propyl	Me	OMe	O
I-6	COONa	Phenyl	Phenyl	Me	Me	S
I-7	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH_2-CH_2-	Me	Me	O
I-8	COOH	Phenyl	(CH_3)2-CH–SO2-CH2-CH2-	Me	OEt	O
I-9	COOH	Phenyl	CH_3-S-CH_2-CH_2-	Me	Et	O
I-10	COONa	Phenyl	Methyl	Me	OMe	O
I-11	COOH	Phenyl	$(CH_3)_2$-CH–SO_2-CH_2-CH_2-	Et	NH–OMe	O
I-12	COOH	Phenyl	n–Propyl	Et	OMe	O
I-13	$COOCH_3$	Phenyl	n–Propyl	Et	Et	O
I-14	COOH	Phenyl	Methyl	Me	OPropyl	S
I-15	COOH	Phenyl	n–Propyl	Me	OPropyl	O
I-16	COOH	Phenyl	n–Butyl	Me	O-*i*-Propyl	O

No.	R^1	R^4, R^5	R^6	R^2	R^3	Z
I-17	COOH	Phenyl	iso-Butyl	OMe	OMe	O
I-18	COOH	Phenyl	iso-Butyl	Me	Me	O
I-19	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH_2-CH_2-	Me	NH-Me	O
I-20	COOH	Phenyl	tert.-Butyl	Et	N-$(Me)_2$	O
I-21	COOH	Phenyl	Cyclopropyl-CH_2-	Me	OMe	O
I-22	COOH	Phenyl	Cyclopentyl	-CH_2-CH_2-CH_2-		O
I-23	COOH	Phenyl	Cyclohexyl	NH-Me	Me	O
I-24	COOH	Phenyl	$(CH_3)_3C$-CH_2-CH_2-	Et	OEt	O
I-25	COOH	Phenyl	3,4-Methylenedioxybenzyl	Et	OMe	S
I-26	COOH	Phenyl	$(CH_3)_2CH$-CH_2-CH_2-CH_2-	CF_3	OMe	O
I-27	COOH	Phenyl	HO_2C-$(CH_2)_2$-	Et	Et	O
I-28	COOH	Phenyl	Cyclopropylmethyl	Me	Me	O
I-29	COOH	Phenyl	H	Me	OMe	O
I-30	COOH	Phenyl	Phenyl	OMe	O-i-Propyl	O
I-31	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH_2-CH_2-	OMe	Me	O
I-32	$COOCH_3$	Phenyl	Phenyl	Me	Me	O
I-33	COOH	Phenyl	4-Isopropyl-Phenyl	Me	OMe	O
I-34	COOH	Phenyl	4-SMe-Phenyl	Me	Me	O
I-35	COOH	Phenyl	4-OMe-Phenyl	Me	Et	O
I-36	COOH	Phenyl	3-Et-Phenyl	CF_3	CF_3	O
I-37	COOH	Phenyl	2-Me-Phenyl	Me	CF_3	O
I-38	COOH	Phenyl	2-Cl-Phenyl	Me	NH-OMe	O
I-39	COOH	2-Me-Phenyl	Methyl	Et	Et	S
I-40	COOH	Phenyl	3-Br-Phenyl	-CH_2-CH_2-CH_2-		O

No.	R^1	R^4, R^5	R^6	R^2	R^3	Z
I-41	COOH	Phenyl	3-NO_2-Phenyl	Me	OMe	O
I-42	COOH	Phenyl	2-HO-Phenyl	Me	O-Propyl	O
I-43	COOH	Phenyl	3,4-Di-OMe-Phenyl	Me	SMe	O
I-44	COOH	Phenyl	3,4-Methylenedioxyphenyl	Me	N-$(Me)_2$	O
I-45	COOH	Phenyl	Methyl	Et	Et	S
I-46	COOH	Phenyl	3,4,5-Tri-OMe-Phenyl	Me	Me	O
I-47	COOH	Phenyl	Benzyl	Me	OMe	O
I-48	COOH	Phenyl	2-Cl-Benzyl	SMe	Me	O
I-49	COOH	Phenyl	3-Br-Benzyl	Me	CF_3	O
I-50	COOH	Phenyl	4-F-Benzyl	Me	OMe	O
I-51	COOH	Phenyl	2-Me-Benzyl	-CH_2-CF_3	OMe	O
I-52	COOH	Phenyl	2-Me-Benzyl	Me	OMe	O
I-53	COOH	Phenyl	3,4-Di-Me-Phenyl-CH_2-CH_2-	Me	Me	O
I-54	COOH	Phenyl	3-Et-Benzyl	Me	N-$(Me)_2$	O
I-55	COOH	Phenyl	4-iso-Propyl-Benzyl	Me	Me	O
I-56	COOH	Phenyl	2,6-Di-OMe-Phenyl-CH_2-CH_2-	Me	OAllyl	O
I-57	COOH	Phenyl	4-OMe-3-Propyl-Benzyl	Me	Et	O
I-58	COOH	Phenyl	2-Me-5-Propyl-Benzyl	Me	OMe	O
I-59	COOH	Phenyl	2-Me-5-Propyl-Benzyl	Et	Et	O
I-60	COOH	Phenyl	4-Me-2-Propyl-Benzyl	Me	OMe	O
I-61	COOH	4-F-Phenyl	Methyl	Me	OMe	O
I-62	$COOCH_3$	4-F-Phenyl	Methyl	Et	Et	O
I-63	COOH	4-Cl-Phenyl	Methyl	Me	OMe	O
I-64	COOH	4-Me-Phenyl	Methyl	Me	OMe	O

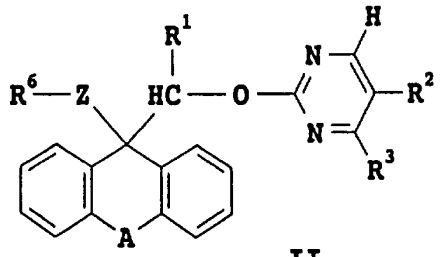
No.	R^1	R^4, R^5	R^6	R^2	R^3	Z
I-65	COOH	4-OMe-Phenyl	Ethyl	Me	NH-OMe	O
I-66	COOH	4-Me-Phenyl	Methyl	Me	Me	O
I-67	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH_2-CH_2-	Et	Et	O
I-68	COOH	3-CF_3-Phenyl	n-Propyl	Me	OMe	O
I-69	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH_2-CH_2-	Et	Me	O
I-70	COOH	4-F-Phenyl	Ethyl	Me	Me	O
I-71	COOH	Phenyl	3-OMe-Phenyl-CH_2-CH_2-	Et	Me	O
I-72	$COOCH_3$	Phenyl	Methyl	Me	OMe	S
I-73	COOH	3-Cl-Phenyl	Ethyl	Me	OEt	O
I-74	COOH	2-F-Phenyl	Methyl	Me	OEt	O
I-75	COOH	2-F-Phenyl	Methyl	Me	Propyl	O
I-76	COOH	2-Me-Phenyl	Methyl	Me	Propyl	O
I-77	COOH	Phenyl	3,4-Di-Cl-Phenyl-CH_2-CH_2-	Me	Propyl	O
I-78	COOH	Phenyl	3,4-Di-Cl-Phenyl-CH_2-CH_2-	Me	OPropyl	O
I-79	COOH	4-CF_3-Phenyl	Methyl	OMe	OMe	O
I-80	COOH	Phenyl	Methyl	Me	OPropyl	O
I-81	COOH	Phenyl	2,6-Di-Cl-Phenyl-CH_2-CH_2-	Et	Allyl	S
I-82	$COOCH_3$	Phenyl	Methyl	Me	O-i-Propyl	O
I-83	COOH	4-OCF_3-Phenyl	n-Propyl	Me	OCF_3	O
I-84	COOH	Phenyl	Propyl	Me	OCF_3	S
I-85	COOH	Phenyl	Methyl	Et	CF_3	O
I-86	COOH	4-F-Phenyl	Benzyl	Me	Me	O
I-87	COOH	Phenyl	3-Cl-Phenyl-CH_2-CH_2-	Et	Me	O
I-88	COOH	Phenyl	4-Cl-Phenyl-CH_2-CH_2-	Me	OMe	O

No.	R^1	R^4, R^5	R^6	R^2	R^3	Z
I-89	COOH	4–Phenyl	3,4-Di-Cl-Phenyl-CH_2-CH_2-	Et	Me	O
I-90	COOH	4–Phenyl	3,4-Di-Cl-Phenyl-CH_2-CH_2-	Me	OMe	O
I-91	COOH	Phenyl	3,5-Di-Cl-Phenyl-CH_2-CH_2-	Et	Et	O
I-92	COOH	Phenyl	3,5-Di-OMe-Phenyl-CH_2-CH_2-	Et	Propyl	O
I-93	COOH	Phenyl	Phenyl	Me	i-Propyl	S
I-94	COOH	Phenyl	3,4-Di-Cl-Phenyl-CH_2-CH_2-	Me	n-Butyl	S
I-95	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH_2-CH_2-	Me	n-Butyl	O
I-96	COOH	Phenyl	3,4-Di-Me-Phenyl-CH_2-CH_2-	Et	Me	O
I-97	COOH	Phenyl	2,5-Di-Cl-Phenyl-CH_2-CH_2-	Me	Ethynyl	O
I-98	COOH	Phenyl	3,4-Di-Et-Phenyl-CH_2-CH_2-	Me	i-Propyl	O
I-99	COOH	4–F–Phenyl	H	Me	OMe	O
I-100	COOH	Phenyl	3,4-Di-Me-Phenyl-CH_2-CH_2-	Et	Me	S
I-101	COOH	Phenyl	4-Isopropylphenyl-CH_2-CH_2-	Me	Me	O
I-102	COOH	4–F–Phenyl	3,4-Di-Me–Phenyl-CH_2-CH_2-	Me	OMe	O
I-103	COOH	Phenyl	Methyl	Me	N-$(Me)_2$	O
I-104	COOH	Phenyl	Methyl	Me	i-Butyl	O
I-105	COOH	Cyclohexyl	Methyl	Me	OMe	O
I-106	COOH	Phenyl	Methyl	Me	OH	O
I-107	$COOCH_3$	Phenyl	iso–Propyl	Me	OMe	O
I-108	$COOC_2H_5$	Phenyl	s-Butyl	Me	Cl	O
I-109	$CONHSO_2$Phenyl	3–CF_3–Phenyl	Methyl	Me	Cl	O
I-110	COOH	Phenyl	2,3-Di-Cl-Phenyl-CH_2-CH_2-	Et	OH	O
I-111	COOH	4–Cl–Phenyl	3,4-Di-Me-Phenyl-CH_2-CH_2-	Me	O-Propyl	O
I-112	COOH	Phenyl	3,4-Di-Et-Phenyl-CH_2-CH_2-	Me	Vinyl	O

No.	R^1	R^4, R^5	R^6	R^2	R^3	Z
I-113	$COOC_2H_5$	Phenyl	Trifluoroethyl	Me	OMe	O
I-114	COOH	Phenyl	HO–CH_2-(HO–CH)–CH_2-	Me	OMe	O
I-115	COOH	Phenyl	HO–CH_2-CH_2-CH_2-	Et	Me	S
I-116	COOH	Phenyl	HO–CH_2-CH_2-CH_2-	Me	OMe	O
I-117	COOH	Phenyl	HO–CH_2-CH_2-CH_2-	Et	OMe	O
I-118	COOH	Phenyl	3–Cl-Phenyl	Me	SMe	S
I-119	COOH	Phenyl	HO–CH_2-CH_2-	Me	SEt	O
I-120	COOH	Phenyl	Phenyl	Me	Allyl	O
I-121	COOH	Phenyl	Phenyl	Me	OAllyl	O
I-122	COOH	Phenyl	Phenyl	CF_3	CF_3	O
I-123	COOH	Phenyl	Phenyl	Et	OMe	O
I-124	COOH	Phenyl	Phenyl	Et	Et	O
I-125	COOH	Phenyl	2-Thiazolyl	Me	OMe	O
I-126	$COOC_2H_5$	3–Cl–Phenyl	Phenyl	Me	O-i-Propyl	O
I-127	$COOC_2H_5$	Phenyl	4-Thiazolyl	Me	Cl	O
I-128	COOH	4–F–Phenyl	Methyl	Ethyl	OMe	O
I-129	$CONHSO_2$Phenyl	4–F–Phenyl	Phenyl	Me	OMe	O
I-130	$COOC_2H_5$	Phenyl	4-Imidazolyl	Me	CF_3	O
I-131	$CONHSO_2$Phenyl	4–CF_3-Phenyl	Phenyl	Me	Cl	O
I-132	$COOCH_3$	Phenyl	4–F-Phenyl	Me	OCF_3	O
I-133	$COOC_2H_5$	Phenyl	2-Dimethylaminophenyl	Me	Me	O
I-134	COOH	Phenyl	n-Pentyl	Me	Me	O
I-135	COOH	Cyclohexyl	Methyl	Me	OPropyl	O
I-136	COOH	Phenyl	Methyl	-CH_2-CH_2-CH_2-		O
I-137	COOH	Phenyl	Phenyl	Me	Me	S

No.	R^1	R^4, R^5	R^6	R^2	R^3	Z
I-138	COOH	3-F-Phenyl	Methyl	Me	SMe	O
I-139	COOH	3-OMe-Phenyl	Methyl	Me	SMe	O
I-140	COOH	Phenyl	Methyl	Et	CF_3	O
I-141	COOH	3-F-Phenyl	Methyl	Me	Me	O
I-142	$CONHSO_2$Phenyl	Phenyl	Methyl	Me	OMe	O
I-143	$CONHSO_2CH_3$	Phenyl	Methyl	Me	Et	O
I-144	COONa	Phenyl	Methyl	Me	OMe	O
I-145	$CONHSO_2CH_3$	Phenyl	Methyl	Me	OMe	O
I-146	Tetrazol	Phenyl	Methyl	Me	OMe	O
I-147	COOH	3-Me-Phenyl	Methyl	OMe	OMe	O
I-148	COOH	4-F-Phenyl	Methyl	Me	SMe	O
I-149	COOH	Phenyl	3,4-Di-Me-Benzyl	Me	OMe	O
I-150	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH_2-CH_2-	-N=CH-N(CH_3)-		O

Table II

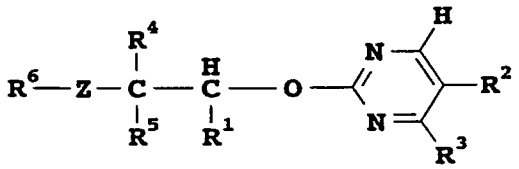


II

No.	R^1	A	R^6	R^2	R^3	Z
II-1	COOH	Linkage	Methyl	Me	OMe	O
II-2	COOH	CH_2	Methyl	Me	OMe	O
II-3	COOH	CH_2-CH_2	Methyl	Me	OMe	O
II-4	COOH	CH=CH	Methyl	Me	OMe	O
II-5	COOH	O	Methyl	Me	OEt	O
II-6	COOH	S	Methyl	Me	OMe	O
II-7	COOH	NH(CH_3)	Methyl	Me	OMe	O
II-8	COOH	Linkage	Isopropyl	Me	OMe	O
II-9	COOH	Linkage	p-Isopropylphenyl	Me	OMe	O
II-10	COOH	Linkage	Benzyl	Me	SMe	O
II-11	COOH	CH=CH	Ethyl	Me	OMe	O
II-12	COOH	CH=CH	$(CH_3)_2$-CH_2-CH_2-	Me	OMe	O
II-13	COOH	CH=CH	Cyclopropyl-CH_2-	Me	OMe	O

We claim:

1. A compound of the formula I



I

in which R^1 is tetrazolyl or a group

in which R has the following meaning:

a) an OR^7 radical in which R^7 is:

hydrogen, the cation of an alkali metal, the cation of an alkaline earth metal, a physiologically tolerated organic ammonium ion such as tertiary C_1-C_4-alkylammonium or the ammonium ion;

C_3-C_8-cycloalkyl, C_1-C_8-alkyl, CH_2-phenyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, hydroxyl, C_1-C_4-alkoxy, mercapto, C_1-C_4-alkylthio, amino, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl)$_2$;

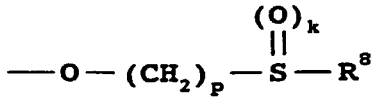
a C_3-C_6-alkenyl or a C_3-C_6-alkynyl group, it being possible for these groups in turn to carry from one to five halogen atoms;

R^7 can also be a phenyl radical which can carry from one to five halogen atoms and/or from one to three of the following radicals: nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, hydroxyl, C_1-C_4-alkoxy, mercapto, C_1-C_4-alkylthio, amino, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl)$_2$;

b) a 5-membered heteroaromatic system, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, which is linked via a nitrogen atom and which may carry from one to two

halogen atoms or from one to two C_1-C_4-alkyl or from one to two C_1-C_4-alkoxy groups;

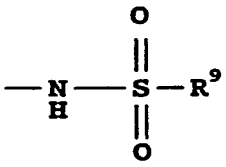
c) a group



in which k has the values 0, 1 and 2, p has the values 1, 2, 3 and 4, and R^8 is

C_1-C_4-alkyl, C_3-C_8-cycloalkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or phenyl which may be substituted by one or more, e.g. from one to three, of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, mercapto, amino, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl)$_2$;

d) a radical



in which R^9 is:

C_1-C_4-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_8-cycloalkyl, it being possible for these radicals to carry a C_1-C_4-alkoxy, C_1-C_4-alkylthio and/or a phenyl radical as mentioned under c);

phenyl which may be substituted by from one to three of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, mercapto, amino, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl)$_2$;

R^2 is hydroxyl, NH_2, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl)$_2$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio or CR^2 forms together with CR^3 a 5- or 6- membered alkylene or alkenylene ring which may be substituted by one or two C_1-C_4-alkyl groups, in which in each case one or more methylene

groups may be replaced by oxygen, sulfur, -NH or $-N(C_1-C_4-alkyl)$;

R^3 is hydroxyl, NH_2, $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$, halogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_3-C_6-alkenyloxy, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, $-NH-O-C_1-C_4$-alkyl, C_1-C_4-alkylthio or CR^3 forms, as indicated under R^2, together with CR^2 a 5- or 6-membered ring;

R^4 and R^5 (which may be identical or different) are:

phenyl or naphthyl, each of which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, amino, $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$; or

phenyl or naphthyl which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or N-alkyl group;

or C_3-C_7-cycloalkyl;

R^6 is hydrogen,

C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl, it being possible for each of these radicals to be substituted one or more times by: hydroxyl, mercapto, carboxyl, halogen, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkylthio, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl, $(C_1-C_4-alkyl)$NHcarbonyl, $(C_1-C_4-alkyl)_2$Ncarbonyl, C_3-C_8-alkylcarbonylalkyl, amino, $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$, phenoxy or phenyl, it being possible for said aryl radicals to be substituted one or more times;

phenyl or naphthyl, each of which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$ or methylenedioxy or ethylenedioxy;

a five- or six-membered heteroaromatic system which contains from one to three nitrogen atoms and/or a sulfur or oxygen atom and which may carry from one to four halogen atoms and/or from one to two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry from one to five halogen atoms and/or from one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

Z is sulfur or oxygen,

and the physiologically tolerated salts, tautomeric forms and the enantiomerically pure and diastereomerically pure forms.

2. The use of compounds I as claimed in claim 1 for treating diseases.

3. The use of compounds I as claimed in claim 1 as endothelin receptor antagonists.

4. The use of compounds I as claimed in claim 1 for producing drugs for treating diseases in which elevated endothelin levels occur.

5. The use of compounds I as claimed in claim 1 for producing drugs for treating diseases in which endothelin contributes to the development and/or progression.

6. The use of compounds I as claimed in claim 1 for treating chronic heart failure, restenosis, high blood pressure, pulmonary hypertension, acute/chronic renal failure, cerebral ischemia, asthma, benign prostate hyperplasia, prostate cancer and acute pancreatitis.

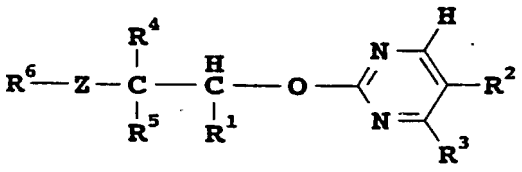
7. A combination of compounds I as claimed in claim 1 and one or more active ingredients selected from inhibitors of the renin-angiotensin system such as renin inhibitors, angiotensin II antagonists, angiotensin converting enzyme (ACE) inhibitors, mixed ACE/neutral endopeptidase (NEP) inhibitors, β-blockers, diuretics, calcium channel blockers and VEGF-blocking substances.

8. A pharmaceutical preparation for oral or parenteral use, comprising at least one compound I as claimed in claim 1 per single dose, in addition to conventional pharmaceutical excipients.

Novel carboxylic acid derivatives with 5,6-substituted pyrimidine ring, their preparation and use as endothelin receptor antagonists

Abstract

Compounds of the formula I



I

where the substituents have the meanings stated in the description, and the use thereof.

PA 9634 US

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL CARBOXYLIC ACID DERIVATIVES WITH 5,6-SUBSTITUTED PYRIMIDINE RING, THEIR PREPARATION AND USE AS ENDOTHELIN RECEPTOR ANTAGONISTS

the specification of which:
[ ] is attached hereto.
[x] was filed on _____ as 10/031,164
[x] was filed as PCT/EP00/06293 on July 5, 2000

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

[ ] In compliance with this duty, attached is an information disclosure statement.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed Yes	No
199 33 164.2	Germany	20 July 1999	[X]	[ ]
Number	Country	Date Filed		

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner

provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Serial No.	Date	Status

I hereby appoint KEIL & WEINKAUF their attorneys and/or agents: Herbert B. Keil, Reg. No. 18,967; Russell E. Weinkauf, Reg. No. 18,495; Gerald H. Bjorge, Reg. No. 32,386; Norman G. Torchin, Reg. No. 34,068; Henry R. Jiles, Reg. No. 32,677; Jason D. Voight, Reg. No. 42,205; George F. Helfrich, Reg. No. 22,350; Ronald H. Smith, Reg. No. 43,679; David C. Liechty, Reg. No. 48,692, the address of all being KEIL & WEINKAUF, 1101 Connecticut Avenue, N.W., Suite 620, Washington, D.C. 20036 (telephone (202)659-0100), with full power to prosecute this application and transact all business in the Patent Office connected therewith.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Wilhelm AMBERG
Full name of first or sole inventor

X [signature] X 13.05.02
Inventor's signature Date

68723 Schwetzingen, Germany DEX German
Residence Citizenship

Schaelzigweg 79, 68723 Schwetzingen, Germany
Post Office Address

****

Georg KETTSCHAU
Full name of second inventor

X Georg Kettschau — X 30/4/2001
Inventor's signature — Date

67071 Ludwigshafen, Germany DEX — German
Residence — Citizenship

Saarburger Strasse 29, 67071 Ludwigshafen, Germany
Post Office Address

****

TOTAL P.05